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61. (New) The recombinant cell of claim 18, wherein the recombinant nucleic acid comprises SEQ ID NO:6.

62. (New) The method of claim 20, wherein the recombinant nucleic acid encodes SEQ ID NO:7.

## REMARKS

Claims 10-20 were pending in the instant application. Claims 10, 11, 13, 14, and 16-20 have been amended and new claims 38-62 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amendments and new claims can be found in the specification of the present application, for example as outlined in the following table:

| CLAIM(S) | SUPPORT IN SPECIFICATION |
|---|---|
| 10, 11, 16, 18, 20 | page 12, lines 28-32; page 25, lines 25-30; page 13, lines 3-5 and 7-8. |
| 13 | page 12, lines 28-32; page 25, lines 25-30; page 13, lines 3-5 and 7-8; page 31, lines 17-21. |
| 14, 17, 19 | page 54, lines 6-8 |
| 38 | page 5, lines 31-34; page 12, lines 28-32; page 25, lines 25-30; page 13, lines 3-8 |
| 39 | page 6, lines 5-14; page 13, lines 3-8; page 26, line 6 |
| 40 | page 30, lines 27-31; page 12, lines 28-32; page 25, lines 25-30; page 26, line 6; page 13, lines 3-8 |
| 41 | page 25, lines 25-28 |
| 42 | page 13, lines 3-8; page 54, lines 6-8; page 26, line 6 |
| 43 | page 13, lines 3-8; page 26, line 6; page 25, lines 25-28 |
| 44 | page 25, lines 25-28 |

| CLAIM(S) | SUPPORT IN SPECIFICATION |
|---|---|
| 45 | page 5, line 36 through page 6, line 4; page 5, lines 27-31; page 13, lines 3-8 |
| 46 | page 5, lines 25-26 |
| 47 | page 24, line 29 |
| 48 | page 24, line 29 |
| 49 | page 30, lines 1-6 |
| 50 | page 25, lines 20-21; page 5, lines 27-31 |
| 51 | page 5, lines 27-31 |
| 52-58 | page 13, lines 3-8 |
| 59, 61 | page 14, lines 7-8 |
| 60, 62 | page 5, lines 27-31 |

No new matter has been added.

Upon entry of the amendments made herein, claims 10-20 and 38-62 will be pending in the present application.

**The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn**

Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the recitation of "reverse complement." In particular, the Examiner states that the claim as currently pending could read on a nucleic acid encoding a "retropeptide" of SEQ ID NO:2 or SEQ ID NO:7.

In response, without agreeing with the Examiner's rejection that the claim lacks definiteness, Applicants have amended claim 16 by deleting the word "reverse." The claim, as amended herein, is directed to a nucleic acid that is hybridizes to the coding strand of a nucleic acid encoding SEQ ID NO:7, *i.e.*, encodes a protein that is closely related to SEQ ID NO:7, which protein is also in the same orientation as SEQ ID NO:7.

**The Rejections Under 35 U.S.C. § 102 Should be Withdrawn**

The Examiner has rejected claim 10 under 35 U.S.C. § 102(b), allegedly as anticipated by Tilman *et al.* (1992, J. Exp. Med. 176:761-779; "Tillman"), Hatano (1997,

Accession Number D50136, "Hatano"), and Allessandrini *et al.* (1991, Mol. Cell. Biol. 11:2096-2107; "Allessandrini"). According to the Examiner, Tillman, Hatano and Allessandrini teach nucleic acids comprising SEQ ID NOS: 12, 13 and 15, respectively. This rejection is obviated for the reasons discussed below.

Applicants have amended claim 10 to recite that the nucleic acid comprises SEQ ID NOS:13, 14, and 15 (which encode S2C6 heavy chain CDRs 8, 9 and 10, respectively) and encodes a protein that binds to CD40. It is axiomatic that for a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, it has to meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In contrast, none of the nucleic acids disclosed by Tillman, Hatano and Allessandrini comprise all three of SEQ ID NOS:13, 14 and 15, nor do the nucleic acids encode a protein that binds to CD40. In particular, the nucleic acid disclosed by Tillman encodes an antibody associated with SLE. The nucleic acid disclosed by Hatano encodes an anti-acid phosphatase light chain. The nucleic acid disclosed by Allessandrini is derived from a D-JH antibody junction.

Accordingly, none of the nucleic acids recited by the Examiner anticipate claim 10 as amended, which is directed to a nucleic acid comprising SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:15 and which encodes a protein that binds to CD40.

Claim 11 is rejected under 35 U.S.C. § 102(b), allegedly as anticipated by Chen *et al.* (1987, J. Biol. Chem. 262:13579-13583; "Chen"), Randen *et al.* (1993, Eur. J. of Immunol. 23:1220-1225; "Randen"), and Singh *et al.* (1991, Lung Research 17:59-567; "Singh"). According to the Examiner, Chen, Randen and Singh teach nucleic acids encoding proteins encoding SEQ ID NOS: 4, 8 and 10, respectively.

In response, Applicants have amended claim 11 to recite that the protein comprises SEQ ID NOS: 8, 9 and 10, which protein binds to CD40. Because it is axiomatic that for a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, it has to meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987), and because none of proteins disclosed by Chen, Randen and Singh comprises all three of SEQ ID NOS:8, 9 and 10 or binds to CD40, the rejection of claim 11 as anticipated by Chen, Randen and Singh cannot stand. In particular, the protein disclosed by Chen is an IgK variant of an

anti-DNA antibody. The protein disclosed by Randen is a synovia Ig rheumatoid factor. The protein disclosed by Singh is a surfactant-associated protein.

Accordingly, none of the nucleic acids recited by the Examiner anticipate claim 11 as amended, which is directed to a nucleic acid encoding a protein comprising SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, and which protein binds to CD40.

In view of the foregoing, Applicants submit that the rejections of claims 10 and 11 under 35 U.S.C. § 102(b) have been obviated and should be withdrawn.

**The Rejection Under 35 U.S.C. § 103 Should be Withdrawn**

I. *The Rejection of Claims 10-14 and 16-20 over Braesch-Anderson in View of de Boer must Be Withdrawn*

Claims 10-14 and 16-20 are rejected under 35 U.S.C. § 103(a), allegedly obvious over Braesch-Anderson et al. (Journal of Immunological Methods, 1986, Vol. 94, pp. 145-151) in view of de Boer (U.S. Patent No. 5,677,165). In particular, according to the Examiner, Braesch-Anderson teaches the hybridoma secreting the S2C6 monoclonal antibody, and de Boer teaches humanized anti-CD40 antibodies 5D12, 3A8, and 3C6 as well as methods of humanizing anti-CD40 antibodies. The Examiner thus concludes that it would have been obvious to one of skill in the art to isolate the nucleic acid encoding the S2C6 antibodies as well as humanize the S2C6 antibody, thereby rendering obvious the presently claimed nucleic acids. Applicants respectfully disagree with the Examiner for the reasons discussed below.

Braesch-Anderson teaches the purification of "S2C6 antigen" from Raji cells using the S2C6 antibody (see, *e.g.*, Braesch-Anderson at page 148 under the header "Affinity Chromatography") and describes biochemical characteristics of the antigen, such as its molecular weight, its isoelectric focusing point, and affinity to con A (see, *e.g.*, Braesch-Anderson at pages 148-149 under the header "Characterization"). Braesch-Anderson demonstrates that S2C6 can be used to purify an "S2C6 antigen" and suggests at page 146, top left column, that the S2C6 antigen may "be suitable for diagnostic and/or prognostic tests of urine or bladder washings" (emphasis added). At best, Braesch-Anderson proposes *in vitro* diagnostics to the S2C6 antigen. Braesch-Anderson, however, provides no suggestion or motivation whatsoever for the skilled artisan to humanize the S2C6 antibody or otherwise clone the DNA encoding it.

de Boer does not remedy the deficiencies of Braesch-Anderson. de Boer describes a class of antibodies, including the monoclonal antibodies 5D12, 3A8 and 3C6, which "bind to a human CD40 antigen on the surface of a human B cell and do not stimulate the growth or differentiation of the B cell." *See, e.g.*, de Boer at column 5, lines 5-8. Although de Boer defines a humanized antibody at column 4, lines 46-49, de Boer does not teach how to humanize either antibodies in general, or CD40 antibodies in particular. However, even assuming, *arguendo*, that de Boer *did* teach the humanization of CD40 antibodies, de Boer does *not*, either alone or in combination with Braesch-Anderson, motivate the skilled artisan to humanize the class of antibodies encoded by the presently claimed nucleic acids.

As stated above, the de Boer antibodies "bind to a human CD40 antigen on the surface of a human B cell and do not stimulate the growth or differentiation of the B cell." In Example 2 of de Boer (at column 14), de Boer describes experiments comparing the effect of the de Boer antibodies and S2C6 on tonsillar B cells in the presence of immobilized IgM and interleukin-2 (IL-2). de Boer demonstrates unequivocally that S2C6, in complete contrast to the de Boer antibodies, was able to stimulate B cell proliferation in either the presence of immobilized IgM (Figure 5A) or IgM plus IL-2 (Figure 5B). Because one seeking to treat cancer looks for reagents that inhibits rather than induces cell proliferation, and because de Boer teaches that S2C6 promotes rather than inhibits proliferation, de Boer could not possibly provide any motivation for the cloning of nucleic acids comprising nucleotide sequences encoding S2C6 CDRs or variable regions of S2C6 and closely related nucleic acids, *i.e.*, the nucleic acids claimed in claims 10-13, 15 or 18, nor their use to produce a protein, as claimed in claim 20.

Further, in contrast to the antibodies encoded by the presently claimed nucleic acids, the de Boer antibodies are characterized in the scientific literature as antibodies that block the binding of CD40 (in the context of B cells) to CD40 ligand (see, *e.g.*, Kwekkeboom *et al.*, 1994, Eur. J. Immunol. 24:508-517, reference CG of the Supplemental Information Disclosure Statement submitted herewith, in particular at Section 3.5 on pages 512-513). Because the de Boer antibodies block the binding of CD40 to CD40 ligand, *i.e.*, do not increase the binding of CD40 ligand to cell surface CD40 on B cells, de Boer could not possibly motivate the skilled artisan to make the nucleic acids of any of claims 14, 16 or 17, because all of these claims are directed to nucleic acids encoding molecules which, *inter alia*,

increase the binding of CD40 ligand to cell surface CD40 on B cells, or to produce a such a protein according to the method claimed in claim 19.

II. *The Rejection of Claims 10, 11, 13, 14, and 16-20 over Katira in View of de Boer must Be Withdrawn*

Claims 10, 11, 13, 14 and 16-20 are also rejected under U.S.C. § 103(a), allegedly as obvious over Katira et al. (Workshop Panel Report in: Schlossman et al., Leukocyte Typing, Vol. V, p. 547) in view of de Boer (U.S. Patent No. 5,677,165). In particular, the Examiner states that Katira teaches a hybridoma that produces the 5C3 monoclonal antibody, which antibody, according to the Examiner, "competes for binding with S2C6 for CD40 receptor and increases the binding of CD40 ligand to CD40 receptor by at least 45%." The Examiner further contends that the teachings of Katira in view of de Boer, characterized as teaching humanized anti-CD40 antibodies 5D12, 3A8, and 3C6 and methods of humanizing anti-CD40 antibodies, render obvious the presently claimed nucleic acids. Applicants respectfully disagree with the Examiner for the reasons discussed below.

The Examiner relies on the teachings of Pound *et al.*, 1999, International Immunology 11:11-20 ("Pound") to recite inherent properties of the 5C3 antibody disclosed in Kitara. Applicants submit, however, that the Examiner has mischaracterized the teachings of Pound in arriving at the instant rejection. Contrary to the Examiner's contention that 5C3 "competes for binding with S2C6 for CD40 receptor," 5C3 does not in any significant way inhibit S2C6 binding to CD40 on B cells (see section entitled "Competitive Binding Studies" at page 13, right column; see also Katira at page 548, section entitled "Epitope Analysis"). In particular, the binding of 5C3 to B cells reduced the binding of S2C6 to CD40 only by approximately 20% (Pound at Table 1, second line of data), indicating that CD40 can simultaneously bind to S2C6 and 5C3, and that, therefore, S2C6 does *not* compete with S2C6 for binding to CD40. This is confirmed by Katira, which summarizes cross-blocking studies between S2C6 and other anti-CD40 antibodies. Katira states at page and Katira at page 548, left column that "[s]ix of the [anti-CD40] mAb blocked by >80 per cent binding of S2C6 to the B cells," the "exceptions were CD40.4 (5C3; average 35 per cent inhibition over three experiments..." Accordingly, the teachings of Pound and Katira indicate that 5C3 does not compete with S2C6 for binding to CD40.

Further, under the experimental conditions described in Pound, S2C6 and 5C3 greatly differed with respect to their effect on the binding of soluble CD40 to membrane-bound CD40 ligand on T cells. Pound describes experiments in which complexes of soluble CD40 (CD40-Fc) preincubated with a test CD40 antibody are assayed for binding to CD40 ligand on activated T cells (see section entitled "Inhibition of binding of soluble CD40 to CD40L on T cells" at page 12, right column). Under these experimental conditions, S2C6 inhibited CD40-Fc binding to CD40 ligand on T cells by approximately 82%, whereas 5C3 increased the binding of CD40-Fc to CD40 ligand on T cells by approximately 32% (Table 1, first line of data; see also Armitage *et al.*, "Distinct patterns of inhibition by CD40 mAb of the CD40 ligand-CD40 interaction", in Leukocyte Typing V, Schlossman et al. (Eds.) 1995; 1:551-552, reference AE of the Information Disclosure Statement, at page Table 1). Although Pound teaches that 5C3 increases the binding of CD40 ligand to soluble CD40 under conditions that S2C6 elicits a completely opposite results (*i.e.*, decreases the binding of CD40 ligand to soluble CD40), nowhere does Pound (or Katira) suggest the cloning or humanization of S2C6 or the isolation of a nucleic acid encoding an antibody that increases the binding of cell surface CD40 on B cells to CD40 by at least 45%.

In view of the foregoing, Applicants submit that Pound and Katira do not, alone or in combination, teach, suggest, or provide the motivation for the presently claimed invention. de Boer does not remedy the deficiencies of Pound and Katira. As discussed above, de Boer teaches a class of antibodies that bind to a human CD40 antigen on the surface of a human B cell, thereby blocking the binding of the CD40 to CD40 ligand, and do not stimulate the growth or differentiation of the B cell. de Boer does not teach, suggest or provide the motivation for isolating nucleic acids encoding S2C6 sequences, or antibodies that increase the binding of cell surface CD40 on B cells to CD40 ligand. Accordingly, de Boer does not, alone or in combination with Pound and/or Katira, render obvious the presently claimed invention.

III. *The Rejection of Claims 10-20 over Braesch-Anderson in View of de Boer and Francisco must Be Withdrawn*

Claims 10-20 are further rejected under 35 U.S.C. § 103(a), allegedly as obvious over Braesch-Anderson et al. (Journal of Immunological Methods, 1986, Vol. 94, pp. 145-151) and de Boer (U.S. Patent No. 5,677,165) and further in view of Francisco et al. (Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169). The Examiner

contends that Braesch-Anderson and de Boer, as discussed above, render claims 10-14 and 16-20 obvious, and that claim 15 is further rendered obvious by Francisco, which teaches a single chain immunotoxin comprising bryodin.

As discussed at length above, neither Braesch-Anderson nor de Boer, individually or in combination, suggest or provide the motivation of the invention claimed in claims 10-14 and 16-20. Francisco, which teaches a single chain immunotoxin comprising bryodin, does not remedy the deficiencies of Braesch-Anderson and de Boer. In particular, the immunotoxin taught by Francisco comprises the variable regions of the anti-CD40 antibody G28-5, an antibody that Applicants have demonstrated to lack any significant effect on the binding of cell surface CD40 on B cells to CD40 ligand (see Section 7.2 at pages 53-54 of the specification, in particular page 54, lines 24-28) and that Pound teaches to be the opposite of S2C6 with respect to its lack of ability to cooperate with soluble, trimeric CD40 ligand to induce DNA synthesis in resting B cells (see Pound at page 14, Section entitled "CD40 epitopes can cooperate to stimulate DNA synthesis" and Table 5). Thus, Francisco does not suggest or provide motivation for cloning the S2C6 antibody or to isolate nucleic acids encoding antibodies that increase the binding of cell surface CD40 on B cells to CD40 ligand, let alone suggest or provide motivation for producing nucleic acids encoding such antibodies fused to bryodin.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 103 are obviated and should be withdrawn.

## CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. In view of the remarks above, it is submitted that all the outstanding rejections have been obviated. Further, it is submitted that the claims are in form for allowance. If any issues remain, the Examiner

is respectfully requested to telephone the undersigned at (212) 790-2247 to discuss any issues or questions.

Respectfully submitted,

Date September 30, 2002

Adriane M. Antler 32,605
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Enclosures

# EXHIBIT A

**EXHIBIT A**
**Attorney Docket No. 9632-014**
**Marked Up Copy of Amended Claims**

10. (Amended) An isolated nucleic acid comprising [SEQ ID NO:1, SEQ ID NO:6, SEQ ID NO:11, SEQ ID NO:12,] SEQ ID NO:13, SEQ ID NO:14, [or] and SEQ ID NO:15, which isolated nucleic acid encodes a protein that binds to CD40.

11. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding a protein comprising [SEQ ID NO:3, SEQ ID NO:4,] SEQ ID NO:8, SEQ ID NO:9, [or] and SEQ ID NO:10, which protein binds to CD40.

13. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding a protein comprising an amino acid sequence that has at least 95% identity to [SEQ ID NO:2 or] SEQ ID NO:7 as determined by use of the BLASTp computer program, which protein binds to CD40.

14. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding a protein, which protein competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110, and which protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%.

16. (Amended) An isolated nucleic acid which hybridizes to the [reverse] complement of a DNA consisting of a coding DNA sequence encoding a protein consisting of [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:2 and] of SEQ ID NO:7, under highly stringent conditions, which isolated nucleic acid encodes a protein that [immunospecifically] binds CD40.

17. (Amended) A recombinant cell containing a recombinant nucleic acid [vector] comprising a nucleotide sequence encoding a protein, which protein competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma deposited with the

ATCC and assigned accession number PTA-110, and which protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%.

18. (Amended) A recombinant cell containing a recombinant nucleic acid [vector] comprising [SEQ ID NO:1, SEQ ID NO:6, SEQ ID NO:11, SEQ ID NO:12,] SEQ ID NO:13, SEQ ID NO:14, [or] and SEQ ID NO:15.

19. (Amended) A method of producing a protein comprising:

(a) growing a cell containing a recombinant nucleic acid [nucleotide sequence] encoding a protein, which protein competes for binding to CD40 with monoclonal antibody S2C6 as deposited with the ATCC and assigned accession number PTA-110, and which protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, such that the protein is expressed by the cell; and

(b) recovering the expressed protein.

20. (Amended) A method of producing a protein comprising:

(a) growing a cell containing a recombinant nucleic acid [nucleotide sequence] encoding a protein comprising [SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:7,] SEQ ID NO:8, SEQ ID NO:9, [or] and SEQ ID NO:10, such that a protein encoded by said nucleotide sequence is expressed by the cell; and

(b) recovering the expressed protein.